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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,310	03/17/2005	Edward H Oldfield	4239-66640-05	7600

36218 7590 05/01/2007

KLARQUIST SPARKMAN, LLP
121 S.W. SALMON STREET
SUITE #1600
PORTLAND, OR 97204-2988

EXAMINER	
CARLSON, KAREN C	

ART UNIT	PAPER NUMBER
1656	

MAIL DATE	DELIVERY MODE
05/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,310	OLDFIELD ET AL.	
	Examiner	Art Unit	
	Karen Cochrane Carlson, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-34 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 1-5, 25-27, 30, 31, 33, and 34 is/are rejected.

7)☒ Claim(s) 6-24,28,29 and 32 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-34 are currently pending and are under examination.

Benefit of priority is to September 24, 2002.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21-23 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 21-23 refer to flow, cannulas, and rates of flow. In Claim 1, none of these variables are set forth. Therefore, these claims are indefinite.

Claim 28 is drawn to the tracer of Claim 26 being a therapeutic agent conjugated to an imaging moiety. It is not clear if this dependent claim calls for two therapeutic agents, ie, the therapeutic agent of Claim 26 plus a therapeutic agent conjugated to an imaging moiety, because the tracer and therapeutic agent are independent in Claim 26.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 25, 26, 27, and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Laske et al. (1997; Tumor regression with regional distribution of the targeted toxin TF-CRM100 in patients with malignant brain tumors. Nature Medicine 3(12): 1362-1368).

Laske et al. teach infusion of therapeutic agent TF-CRM107 into brain tumors via convection enhanced delivery. In Table 2, footnote 1 states:

"Tf-CRM107 concentration was initially kept constant at 0.1 ug/ml while the volume was escalated to 40 ml to improve drug distribution as assessed by MRI".

Laske et al. used gadolinium-enhanced T1-weighted MRI scans – see Fig 1.

Thus, while this disclosure is in a footnote identifying pre-study experiments that led to using the infusion variables found in the study, it appears that Laske et al. used a tracer (Gd; **Claim 5, 30**) with the therapeutic agent TF-CRM107 to monitor the distribution of the solution in the brain (**Claim 25, 27**) by imaging via MRI (**Claim 4**) the tracer (**Claim 1**), and ceased the delivery when the volume reached 40ml (**Claim 2, 26**) at the target tissue (**Claim 3**).

Claim 30 is rejected under 35 U.S.C. 102(b) as being anticipated by Uggeri et al. (USP 5,660,814, issued August 26, 1997).

Uggeri et al. teach tracers comprising gadolinium – see Col. 5, line 36, 37, for example. See the entire patent for paramagnetic chelates as contrasting agents.

Claims 30 and 34 are rejected under 35 U.S.C. 102(b) as being anticipated by Kobayashi et al. (July 1, 2001; Dynamic micro-magnetic resonance imaging of liver micro-metastasis in mice with a novel liver macromolecular magnetic resonance contrast agent DAB-AM64-(1B4M-Gd)$_{64}$. Cancer Research 61: 4966-4970).

Kobayashi et al. teach DAB-AM64-(1B4M- Gd)$_{64}$ at page 4966, rt col., last para.

Claims 30 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Wisneski et al. (1985 ; Absence of myocardial biochemical toxicity with a non ioninc contrast agent iopamidol. American Heart Journal 110 (3): p609-617; only the abstract is being provided).

Wisneski et al. teach contrast agent iopamidol.

Claims 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Wosilait et al. (1981; Competition between serum albumin and soluble fraction of liver for binding of warfarin and other drugs. Res Commun. Chem Pathol Pharamcol. 32(1): 113-122; only the abstract is being provided).

Wosilait et al. teach iopanoic acid binding to human serum albumin (HAS) because iopanoic acid displaced warfarin from HSA. Therefore, Wosilait et al. teach albumin conjugated to iopanoic acid.

Claims 30 31, 33, and 34 drawn to kits comprising tracers are included in the rejections above. In *In re Haller,* 73 USPQ 403 (CCPA 1946), the Court held that an old compound, packaged and labeled to show its use, is not patentable. The packaging of a known compound and the application of an appropriate label thereto does not involved invention over the known compound.

Claims 6-24, 28, 29, and 32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Art of Record:

Kroll et al. (1996; Increasing volume of distribution to the brain with interstitial infusion: Dose, rather than convection, might be the most important factor. Neurosurgery 38(4): 746-754) teach convection enhances deliver of the tracer MION into rat brain for up to 25 minutes (page 747, rt col., mid para. 1). MRI was performed at 2.5 hrs after the beginning of the infusion (page 747, rt col., para. 2). Therefore, Kroll et al. do not teach imaging during the delivery of MION into

rat brain, and do not teach or suggest to include therapeuric agents in the solution comprising the tracer.

Lonser et al. (1998; Direct convective delivery of macromolecules to the spinal cord. J. Neurosurgery 89: 616-622) teach convection deliver of the tracer Gd-labeled biotinylated human serum albumin into the spinal cords of pigs or monkeys (page 617, rt col., para. 2). Lonser et al. used MRI after the removal of the cannula to determine the volume of distribution (page 618, rt col., para. 2, 3). Therefore, Lonser et al. do not teach imaging during the delivery of Gd-labeled biotinylated human serum albumin into the spinal cords, and do not teach or suggest to include therapeuric agents in the solution comprising the tracer.

Weissleder et al. (USP 5,514,379, issued May 7,1996) teach hydrogels comprising tracer Gd: diethylenetriamine-pentaacetic acid (DPTA; a dendrimer): serum albumin tracer and therapeuric agents such as doxorubicin (Col. 11, line 27 and para. 4) and monitoring the delivery with MRI. Weissleder et al. do not teach or suggest convection enhanced delivery of a solution comprising the tracer and therapeutic agent.

Laske et al. (USP 5,720,720 issued February 24, 1998) teach convection enhanced delivery of indium111-transferrin into the corona radiata of cat brain using stereotaxic coordinates (col. 13, 14). Laske et al. did not monitor the distribution of In111-Tf via imaging but via autoradiography after euthanasia of the cats (Col. 14, para. 4 and Figs 9A,B). Laske et al. do not teach or suggest to co-administer the tracer and a therapeutic agent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Cochrane Carlson, Ph.D. whose telephone number is 571-272-0946. The examiner can normally be reached on 7:00 AM - 4:00 PM, off alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen Cochrane Carlson PhD

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KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER